Pre-eclampsia, eclampsia, and hypertension

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ABSTRACT

INTRODUCTION: Pre-eclampsia (raised blood pressure and proteinuria) complicates 2% to 8% of pregnancies, and increases morbidity and mortality in the mother and child. Pre-eclampsia is more common in women with multiple pregnancy and in those who have conditions associated with microvascular disease. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of preventive interventions in women at risk of pre-eclampsia? What are the effects of interventions in women who develop mild to moderate hypertension during pregnancy? What are the effects of interventions in women who develop severe pre-eclampsia or very high blood pressure during pregnancy? What is the best choice of anticonvulsant for women with eclampsia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 69 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticonvulsants, antihypertensive drugs, antioxidants, antiplatelet drugs, atenolol, bed rest, hospital admission, or day care, calcium supplementation, choice of analgesia during labour, early delivery (interventionist care), evening primrose oil, fish oil, glyceryl trinitrate, magnesium supplementation, plasma volume expansion, and salt restriction.

QUESTIONS

INTERVENTIONS

PREVENTION OF PRE-ECLAMPSIA

Beneficial

Unknown effectiveness

Unlikely to be beneficial

TREATMENTS FOR MILD–MODERATE HYPERTENSION

Unknown effectiveness

TREATMENT OF SEVERE EPISODES OF PRE-ECLAMPSIA

Beneficial

Likely to be beneficial

Unknown effectiveness

ECLAMPSIA: ANTICONVULSANTS

Beneficial

To be covered in future updates

Interventions in women with pre-existing hypertension

Treatment of postpartum hypertension

Footnote

*There is consensus that women with severe hypertension during pregnancy should have antihypertensive treatment and that women with eclampsia should have an anticonvulsant. Placebo-controlled trials would, therefore, be unethical.

Key points

- Pre-eclampsia (raised blood pressure and proteinuria) complicates 2% to 8% of pregnancies, and increases morbidity and mortality in the mother and child.

  Pre-eclampsia is more common in women with multiple pregnancy and in those with conditions associated with microvascular disease.

- Antiplatelet drugs (primarily low-dose aspirin) reduce the risk of pre-eclampsia, death of the baby, and premature birth without increasing the risks of bleeding, in women at high risk of pre-eclampsia.

  Calcium supplementation reduces the risk of pre-eclampsia compared with placebo.

  We don't know whether fish oil, evening primrose oil, salt restriction, magnesium supplementation, or glyceryl trinitrate are beneficial in high-risk women because there are insufficient data to draw reliable conclusions. We don't know whether antioxidants reduce rates of pre-eclampsia as the data are inconsistent, although they are unlikely to reduce mortality.

- We don't know whether atenolol reduces the risk of pre-eclampsia, but it may worsen outcomes for babies.

- For women with mild to moderate hypertension during pregnancy, antihypertensive drugs reduce the risk of progression to severe hypertension, but may not improve other clinical outcomes.

  ACE inhibitors have been associated with fetal renal failure, and beta-blockers are associated with the baby being born small for its gestational age.

  We don't know whether bed rest or hospital admission are also beneficial.

- There is consensus that women who develop severe hypertension in pregnancy should receive antihypertensive treatment, but we don't know which antihypertensive agent is most effective.

  We don't know whether plasma volume expansion, antioxidants, epidural analgesia, or early delivery improve outcomes for women with severe pre-eclampsia.

- Magnesium sulphate reduces the risk of first or subsequent seizures in women with severe pre-eclampsia compared with placebo.

- Magnesium sulphate reduces the risk of subsequent seizures in women with eclampsia compared with either phenytoin or diazepam, with fewer adverse effects for the mother or baby.

Clinical context

DEFINITION

Hypertension during pregnancy may be associated with one of several conditions. **Pregnancy-induced hypertension** or **gestational hypertension** is a rise in blood pressure, without proteinuria, during the second-half of pregnancy. **Pre-eclampsia** is a multisystem disorder, unique to pregnancy, that is usually associated with raised blood pressure and proteinuria. It rarely presents before 20 weeks' gestation. **Eclampsia** is one or more convulsions in association with the syndrome of pre-eclampsia. **Pre-existing hypertension** (not covered in this review) is known hypertension before pregnancy, or raised blood pressure before 20 weeks' gestation. It may be essential hypertension or, less commonly, secondary to an underlying disease. [1]

INCIDENCE/ PREVALENCE

Pregnancy-induced hypertension affects 10% of pregnancies, and pre-eclampsia complicates 2% to 8% of pregnancies. [2] Eclampsia occurs in about 1/2000 deliveries in resource-rich countries. [3] In resource-poor countries, estimates of the incidence of eclampsia vary from 1/100 to 1/1700. [4] [5]

AETIOLOGY/ RISK FACTORS

The cause of pre-eclampsia is unknown. It is likely to be multifactorial, and may result from deficient placental implantation during the first-half of pregnancy. [6] Pre-eclampsia is more common among women likely to have a large placenta (such as those with multiple pregnancy) and among women with medical conditions associated with microvascular disease (such as diabetes, hypertension, and collagen vascular disease). [7] [8] One systematic review found that the risk of pre-eclampsia is increased in women with a previous history of pre-eclampsia (RR 7.19, 95% CI 5.85 to 8.83) and in those with antiphospholipid antibodies (RR 9.72, 95% CI 4.34 to 21.75), pre-existing diabetes (RR 3.56, 95% CI 2.54 to 4.99), multiple (twin) pregnancy (RR 2.93, 95% CI 2.04 to 4.21), nulliparity (RR 2.91, 95% CI 1.28 to 6.61), family history (RR 2.90, 95% CI 1.70 to 4.93), raised blood pressure (diastolic 80 mm Hg or greater) at booking (RR 1.38, 95 % CI 1.01 to 1.87), raised body mass index before pregnancy (RR 2.47, 95% CI 1.66 to 3.67) or at booking (RR 1.55, 95% CI 1.28 to 1.88), or maternal age 40 years or older (RR 1.96, 95% CI 1.34 to 2.87, for multiparous women). The review reported that other factors that increase the risk are: an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease, and chronic hypertension. [9] A second systematic review of the accuracy of 27 predictive tests for pre-eclampsia found that some seemed to have high specificity, but at the expense of compromised sensitivity. [10] The review reported that tests with specificity >90% were: body mass index >34, alpha-fetoprotein, and uterine

artery Doppler (bilateral notching). The review found the only Doppler test with a sensitivity of >60% was resistance index and combinations of indices. It also found that a few tests not commonly seen in routine practice (kallikreinuria and SDS-PAGE proteinuria) potentially have both high sensitivity and specificity, but these require further investigation. [10] Cigarette smoking seems to be associated with a lower risk of pre-eclampsia, but this potential benefit is outweighed by an increase in adverse outcomes such as low birth weight, placental abruption, and perinatal death. [11]

PROGNOSIS

The outcome of pregnancy in women with pregnancy-induced hypertension alone is at least as good as that for normotensive pregnancies. [7] [12] However, once pre-eclampsia develops, morbidity and mortality increase for both mother and child. For example, perinatal mortality for women with severe pre-eclampsia is double that for normotensive women. [7] Perinatal outcome is worse with early gestational hypertension. [7] [12] [13] Perinatal mortality also increases in women with severe essential hypertension. [14]

AIMS OF INTERVENTION

To delay or prevent the development of pre-eclampsia and eclampsia, and to improve outcomes for women and their children. Once pre-eclampsia has occurred, to minimise morbidity and mortality for women and their children, and to ensure that health service resources are used appropriately.

OUTCOMES

For the woman: mortality, **morbidity** (such as renal failure, coagulopathy, cardiac failure, liver failure, placental abruption, and stroke), **development of pre-eclampsia** (rates of severe hypertension, rates of pre-eclampsia, proteinuria, and hypertension), **seizures** (eclampsia) and **need for further interventions** (caesarean section); **use of resources** (such as dialysis, ventilation, admission to intensive care, or length of stay); **adverse effects** of treatment. **For the child: mortality**, intrauterine growth restriction, **preterm birth**, and **morbidity** (such as intraventricular haemorrhage, respiratory distress syndrome, or asphyxia, small for gestational age); measures of infant and **child development** (such as cerebral palsy or significant learning disability); **use of resources** (such as admission to a special care nursery, ventilation, length of stay in hospital, and special needs in the community); **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal February 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2010, Embase 1980 to February 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 1 (1966 to date of issue). When editing this review we used The Cochrane Database of Systematic Reviews 2010, Issue 1. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single-blinded, and containing any number of individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 53). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of preventive interventions in women at risk of pre-eclampsia?

OPTION ANTIPLATELET DRUGS

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- Antiplatelet drugs (primarily low-dose aspirin) reduce the risk of pre-eclampsia, death of the baby, and premature birth without increasing the risks of bleeding, in women at high risk of pre-eclampsia.

Benefits and harms

Antiplatelet drugs versus placebo:

We found one systematic review (search date 2006, 59 RCTs, 37,560 women) [15] using aggregate data and one systematic review using data from individual patients (search date 2006, 31 RCTs, 32,217 women). [16]

Mortality

Compared with placebo/no antiplatelet drugs Antiplatelet agents seem more effective at reducing the rate of perinatal mortality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infant mortality					
[15] Systematic review	33,098 women at risk of pre-eclampsia 40 RCTs in this analysis	**Infant mortality** 414/16,607 (2.5%) with antiplatelet agents 475/16,491 (2.9%) with control Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel	RR 0.86 95% CI 0.76 to 0.98 NNT 243 95% CI 131 to 1666	●○○	antiplatelet agents
[16] Systematic review	30,672 women 23 RCTs in this analysis	**Fetal/baby death before discharge** 484/15,412 (3.1%) with antiplatelet agents 524/15,260 (3.4%) with control Antiplatelet agent used was mainly aspirin	RR 0.91 95% CI 0.81 to 1.03	⟷	Not significant

Morbidity

Compared with placebo/no antiplatelet drugs Antiplatelet agents are more effective at reducing the number of babies that need ventilation or that are born small for their gestational age, but are no more effective at reducing abruption rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal morbidity					
[16] Systematic review	24,343 women 16 RCTs in this analysis	**Abruption** 115/12,213 (0.9%) with antiplatelet agents 97/12,130 (0.8%) with control Antiplatelet agent used was mainly aspirin	RR 1.13 95% CI 0.87 to 1.48 P value not reported	⟷	Not significant
Infant morbidity					
[16] Systematic review	7377 women 9 RCTs in this analysis	**Number of infants ventilated** 208/3715 (6%) with antiplatelet agents 250/3662 (7%) with control Antiplatelet agent used was mainly aspirin	RR 0.79 95% CI 0.67 to 0.95 P = 0.05	●○○	antiplatelet agents
[15] Systematic review	23,638 women at risk of pre-eclampsia 36 RCTs in this analysis	**Babies born small for gestational age** 983/11,904 (8%) with antiplatelet agents 1062/11,734 (9%) with control	RR 0.90 95% CI 0.83 to 0.98	●○○	antiplatelet agents

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel			

Development of pre-eclampsia

Compared with placebo/no antiplatelet drugs Antiplatelet agents (mainly low-dose aspirin) are more effective at reducing pre-eclampsia in women at risk of pre-eclampsia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rates of pre-eclampsia					
[15] Systematic review	32,590 women at risk of pre-eclampsia 46 RCTs in this analysis	**Proportion of women with pre-eclampsia** 1081/16,396 (7%) with antiplatelet agents 1292/16,194 (8%) with control Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel	RR 0.83 95% CI 0.77 to 0.89 NNT 72 95% CI 52 to 119	●○○	antiplatelet agents
[16] Systematic review	30,822 women at risk of pre-eclampsia 24 RCTs in this analysis	**Risk of pre-eclampsia** 1221/15,481 (8%) with antiplatelet agents 1340/15,341 (9%) with control Antiplatelet agent used was mainly aspirin	RR 0.90 95% CI 0.84 to 0.97 P = 0.004	●○○	antiplatelet agents
[15] Systematic review	4121 women at high risk of pre-eclampsia 18 RCTs in this analysis Subgroup analysis	**Proportion of women with pre-eclampsia** 323/2070 (16%) with antiplatelet agents 425/2051 (21%) with control Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel	RR 0.75 95% CI 0.66 to 0.85	●○○	antiplatelet agents
[15] Systematic review	28,469 women at moderate risk of pre-eclampsia Subgroup analysis	**Proportion of women with pre-eclampsia** 758/14,326 (5%) with antiplatelet agents 867/14,143 (6%) with control Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel	RR 0.86 95% CI 0.79 to 0.95	●○○	antiplatelet agents
[15] Systematic review	Women at moderate to high risk of pre-eclampsia (absolute number not reported) 16 RCTs in this analysis Subgroup analysis	**Proportion of women with pre-eclampsia** with >75 mg aspirin with control Absolute results not reported	RR 0.64 95% CI 0.51 to 0.80	●○○	>75 mg aspirin
[15] Systematic review	Women at moderate to high risk of pre-eclampsia (absolute number not reported) 5 RCTs in this analysis	**Proportion of women with pre-eclampsia** with >75 mg aspirin plus dipyridamole with control Absolute results not reported	RR 0.30 95% CI 0.15 to 0.60	●●○	>75 mg aspirin plus dipyridamole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis				
[15] Systematic review	Women at moderate to high risk of pre-eclampsia (absolute number not reported) 21 RCTs in this analysis Subgroup analysis	**Proportion of women with pre-eclampsia** with 75 mg aspirin or less with control Absolute results not reported	RR 0.88 95% CI 0.81 to 0.95	●○○	75 mg aspirin or less

Preterm birth

Compared with placebo/no antiplatelet drugs Antiplatelet drugs (mainly low-dose aspirin) are more effective at reducing the risk of babies being born before 34 and 37 weeks. However, antiplatelet drugs do not reduce the risk of babies being born before 28 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[15] Systematic review	31,151 women at risk of pre-eclampsia 29 RCTs in this analysis	**Premature birth** 2612/15,629 (17%) with antiplatelet agents 2797/15,522 (18%) with control Antiplatelet agents used were mainly aspirin, but also dipyridamole and ozagrel	RR 0.92 95% CI 0.88 to 0.97 NNT 72 95% CI 52 to 119	●○○	antiplatelet agents
[16] Systematic review	31,232 women 26 RCTs in this analysis	**Birth before 34 weeks** 1018/15,709 (6%) with antiplatelet agents 1111/15,523 (7%) with control Antiplatelet agent used was mainly aspirin	RR 0.90 95% CI 0.83 to 0.98 P value not reported	●○○	antiplatelet agents
[16] Systematic review	31,315 women 26 RCTs in this analysis	**Number of births <37 weeks** 2649/15,749 (17%) with antiplatelet agents 2799/15,567 (18%) with control Antiplatelet agent used was mainly aspirin	RR 0.93 95% CI 0.89 to 0.98 P = 0.05	●○○	antiplatelet agents
[16] Systematic review	30,001 women 26 RCTs in this analysis	**Preterm birth <28 weeks** 291/15,082 (1.9%) with antiplatelet agents 331/14,919 (2.2%) with control Antiplatelet agent used was mainly aspirin	RR 0.87 95% CI 0.75 to 1.02	⟷	Not significant

Need for further interventions

Compared with placebo/no antiplatelet drugs Antiplatelet agents are no more effective at reducing the rate of caesarean section (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for further intervention					
[16] Systematic review	29,117 women 23 RCTs in this analysis	**Caesarean delivery** 3362/14,652 (23%) with antiplatelet agents 3175/14,465 (22%) with control Antiplatelet agent used was mainly aspirin	RR 1.03 95% CI 0.99 to 1.08	⟷	Not significant

No data from the following reference on this outcome. [15]

Use of resources

Compared with placebo/no antiplatelet drugs Antiplatelet agents are no more effective at reducing the number of babies admitted to SCU/NICU (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Use of resources					
[16] Systematic review	30,097 women 18 RCTs in this analysis	**SCU/NICU admission** 2385/15,082 (15.8%) with antiplatelet agents 2456/15,015 (16.3%) with control Antiplatelet agent used was mainly aspirin	Reported as non-significant RR not reported	⟷	Not significant

No data from the following reference on this outcome. [15]

Seizures

No data from the following reference on this outcome. [15] [16]

Child development

No data from the following reference on this outcome. [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] Systematic review	17,382 women 13 RCTs in this analysis	**Pregnancy with any serious adverse outcome** 1552/8684 (18%) with antiplatelet agents 1716/8698 (20%) with control Antiplatelet agent used was mainly aspirin	RR 0.90 95% CI 0.85 to 0.96 P value not reported	●○○	antiplatelet agents

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] Systematic review	Women at risk of pre-eclampsia (number not reported)	**Maternal or infant bleeding** with aspirin with control Absolute results not reported	The systematic review found no evidence that aspirin increased the risk of bleeding for mother or baby	⟷	Not significant
[16] Systematic review	29,146 women 15 RCTs in this analysis	**Infant bleeding** 287/14,583 (1.9%) with antiplatelet agents 308/14,563 (2.1%) with control Antiplatelet agent used was mainly aspirin	RR 0.93 95% CI 0.80 to 1.09 P value not reported	⟷	Not significant
[17] [18] RCT	Infants of women at risk of pre-eclampsia (number not reported)	**Treatment-related developmental complications , 12 to 18 months** with aspirin with placebo Absolute results not reported	Two observational studies followed up children of mothers enrolled in RCTs comparing aspirin versus placebo for 12 to 18 months. They found no significant difference between aspirin and placebo in children of mothers treated for: hospital visits for congenital malformations, motor deficit, developmental delay, respiratory problems, or bleeding problems; height or weight below the third centile; or bleeding rates	⟷	Not significant

Further information on studies

[15] [16] Almost all RCTs used low-dose aspirin (50–75 mg/day) and most were placebo-controlled. The RCTs included women with a variety of risk factors (including a history of previous early-onset disease, diabetes, or chronic hypertension) and were conducted in both resource-rich and resource-poor countries. Women were categorised as high risk if they had previous severe pre-eclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease. The number-needed-to-treat (NNT) values cannot be applied directly to different populations of women; the values stated represent estimates for women with a risk of pre-eclampsia that is an average over all the participants in the RCTs. The absolute benefit was higher (and the NNT lower) in women at higher risk of pre-eclampsia.

Comment: None.

OPTION CALCIUM SUPPLEMENTATION

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- Calcium supplementation reduces the risk of pre-eclampsia compared with placebo.

Benefits and harms

Calcium supplementation versus placebo:

We found one systematic review (search date 2006, 12 RCTs, 15,206 women; [19] see comment below) and one additional RCT. [20]

Mortality

Compared with placebo Calcium supplements seem more effective at reducing the risk of maternal death or serious morbidity; however, they seem no more effective at reducing stillbirth or death of the baby before discharge from hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal death or serious morbidity					
[19] Systematic review	9732 women 4 RCTs in this analysis	**Maternal mortality/serious morbidity** 167/4856 (3%) with calcium supplementation (mainly 1.5–2 g/day) 210/4876 (4%) with placebo	RR 0.80 95% CI 0.65 to 0.97	●○○	calcium supplementation
Stillbirth or neonatal death before discharge					
[19] Systematic review	15,141 women 10 RCTs in this analysis	**Stillbirth or death of the baby before hospital discharge** with calcium supplementation (mainly 1.5–2 g/day) with placebo Absolute results not reported	RR 0.89 95% CI 0.73 to 1.09	⟷	Not significant
[20] RCT	590 low-risk women in their first pregnancy	**Still birth** 6/273 (2.2%) with elemental calcium (2 g) 5/251 (2.0%) with placebo	P = 0.62	⟷	Not significant

Morbidity

Compared with placebo Calcium supplementation seems no more effective at reducing the number of babies born with a birth weight of below 2500 g (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infant morbidity					
[19] Systematic review	14,359 women 8 RCTs in this analysis	**Birth weight <2500 g** with calcium supplementation (mainly 1.5–2 g/day) with placebo Absolute results not reported	RR 0.84 95% CI 0.68 to 1.03	⟷	Not significant

No data from the following reference on this outcome. [20]

Development of pre-eclampsia

Compared with placebo Calcium supplements are more effective at reducing the risk of pre-eclampsia, especially in women with low dietary calcium (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[19] Systematic review	15,206 women 12 RCTs in this analysis	**Pre-eclampsia** 368/7578 (5%) with calcium supplementation (mainly 1.5–2 g/day) 480/7628 (6%) with placebo	RR 0.48 95% CI 0.33 to 0.69	●●○	calcium supplementation
[19] Systematic review	10,154 women with low dietary calcium Subgroup analysis	**Pre-eclampsia** 198/5058 (4%) with calcium supplementation (mainly 1.5–2 g/day) 276/5096 (5%) with placebo	RR 0.36 95% CI 0.18 to 0.70	●●○	calcium supplementation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	5022 women with normal dietary calcium Subgroup analysis	**Pre-eclampsia** 169/2505 (7%) with calcium supplementation (mainly 1.5–2 g/day) 197/2517 (8%) with placebo	RR 0.62 95% CI 0.32 to 1.20	⟷	Not significant
[20] RCT	590 low-risk women in their first pregnancy	**Pre-eclampsia , up to delivery** 11/273 (4%) with elemental calcium (2 g) 30/251 (12%) with placebo	OR 0.31 95% CI 0.15 to 0.63 P = 0.001 66/590 (11%) women were lost to follow-up	●●○	elemental calcium

Preterm birth

Compared with placebo Calcium supplementation may be no more effective at reducing preterm birth (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[19] Systematic review	14,751 women 10 RCTs in this analysis	**Preterm birth** with calcium supplementation (mainly 1.5–2 g/day) with placebo Absolute results not reported	RR 0.81 95% CI 0.64 to 1.03	⟷	Not significant
[20] RCT	590 low-risk women in their first pregnancy	**Preterm birth** 19/273 (7%) with elemental calcium (2 g) 32/251 (13%) with placebo	P = 0.03 66/590 (11%) women were lost to follow-up	○○○	elemental calcium

Need for further interventions

Compared with placebo Calcium supplements seem no more effective at reducing the risk of caesarean delivery (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Caesarean delivery					
[19] Systematic review	14,710 women 7 RCTs in this analysis	**Caesarean delivery** with calcium supplementation (mainly 1.5–2 g/day) with placebo Absolute results not reported	RR 0.95 95% CI 0.88 to 1.01	⟷	Not significant
[20] RCT	590 low-risk women in their first pregnancy	**Caesarean delivery** 41/273 (15%) with elemental calcium (2 g) 27/251 (11%) with placebo	P = 0.15 66/590 (11%) women were lost to follow-up	⟷	Not significant

Seizures

No data from the following reference on this outcome. [19] [20]

Use of resources

No data from the following reference on this outcome. [19] [20]

Child development

No data from the following reference on this outcome. [19] [20]

Adverse effects

No data from the following reference on this outcome. [19] [20]

Further information on studies

[19] Most trials in the systematic review were of good quality and included nulliparous or primiparous women. They were conducted largely in the USA and South America. They included mainly women at low risk, with low dietary calcium. Several studies reported that adherence to treatment was 60% to 90%. The proportion of women taking 90% to 100% of all allocated treatment was 85% in the largest study, but low in several others (20% in 1 study). The statistical heterogeneity for some outcomes seemed to be explained by differences between the small and large trials, with small trials of largely high-risk women having more positive results.

[20] The additional trial was conducted in India.

Comment: None.

OPTION ANTIOXIDANTS

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether antioxidants reduce rates of pre-eclampsia as the data are inconsistent, although they are unlikely to reduce mortality.

Benefits and harms

Antioxidants versus placebo:

We found one systematic review (search date 2007, 10 RCTs, 6533 women) of antioxidant treatment (largely either the combination of vitamins C and E or antioxidant minerals, such as selenium); [21] one systematic review (search date 2006, 4 RCTs, 4680 women) reporting solely on the combination of antioxidant vitamins C plus E; [22] one small subsequent RCT of multiple antioxidant vitamins and minerals; [23] one small RCT of lycopene; [24] one small trial of coenzyme Q10; [25] and two large trials of the vitamins C and E. [26] [27]

Mortality

Compared with placebo/no antioxidant Vitamin C plus E seems no more effective at reducing perinatal deaths (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Perinatal mortality					
[21] Systematic review	5144 women 4 RCTs in this analysis	**Perinatal mortality** 77/2569 (3.0%) with antioxidants 69/2575 (2.7%) with no antioxidants	RR 1.12 95% CI 0.81 to 1.53	⟷	Not significant
[22] Systematic review	4680 women 4 RCTs in this analysis	**Infant mortality** 2.6% with vitamins C and E 2.3% with placebo Absolute results reported graphically	RR 1.10 95% CI 0.78 to 1.56	⟷	Not significant
[26] RCT	739 women diagnosed with chronic hypertension or a prior history of pre-eclampsia between 12 to 19 weeks' gestation	**Perinatal mortality** 18/356 (5.1%) with vitamin C (1000 mg/day) plus vitamin E (400 IU/day) 19/352 (5.4%) with placebo	RR 1.00 95% CI 0.53 to 1.87	⟷	Not significant
[27] RCT	1365 women between 14 to 22 weeks' gestation	**Perinatal mortality** with vitamin C (1000 mg/day) plus vitamin E (400 IU/day) with placebo	RR 0.8 95% CI 0.6 to 1.2	⟷	Not significant

No data from the following reference on this outcome. [23] [24] [25]

Morbidity

Compared with placebo/no antioxidant Antioxidants seem no more effective at reducing the number of babies born small for their gestational age (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infant morbidity					
[21] Systematic review	5271 women 5 RCTs in this analysis	**Baby small for gestational age** 532/2626 (20.2%) with antioxidants 532/2645 (20.1%) with no antioxidants	RR 0.83 95% CI 0.51 to 1.11	⟷	Not significant
[22] Systematic review	4860 women 4 RCTs in this analysis	**Baby small for gestational age** 21% with vitamins C and E 20% with placebo Absolute results reported graphically	RR 0.94 95% CI 0.74 to 1.19	⟷	Not significant

No data from the following reference on this outcome. [23] [24] [25] [26] [27]

Development of pre-eclampsia

Compared with placebo/no antioxidant We don't know whether antioxidants are more effective at reducing the risk of pre-eclampsia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[21] Systematic review	5456 women 9 RCTs in this analysis	**Pre-eclampsia** 272/2701 (10%) with antioxidants 314/2755 (11%) with no antioxidants	RR 0.73 95% CI 0.51 to 1.06	⟷	Not significant
[22] Systematic review	4680 women 4 RCTs in this analysis	**Pre-eclampsia** 11.0% with vitamins C and E 11.4% with placebo Absolute results reported graphically	RR 0.97 95% CI 0.82 to 1.13	⟷	Not significant
[23] RCT	60 women	**Pre-eclampsia** 2/29 (7%) with antioxidants 9/31 (29%) with placebo	P = 0.04	○○○	antioxidants
[24] RCT	159 women with singleton pregnancy	**Pre-eclampsia** 14/77 (18.2%) with lycopene 15/82 (18.3%) with placebo	P = 0.99	⟷	Not significant
[25] RCT	235 women at increased risk of pre-eclampsia	**Pre-eclampsia** 17/80 (21%) with coenzyme Q10 (CoQ10) 200 mg daily from 20 weeks' gestation 30/74 (41%) with placebo	RR 0.56 95% CI 0.33 to 0.96	●○○	CoQ10
[26] RCT	739 women diagnosed with chronic hypertension or a prior history of pre-eclampsia between 12 to 19 weeks' gestation	**Pre-eclampsia** 49/355 (15%) with vitamin C (1000 mg/day) plus vitamin E (400 IU/day) 55/352 (16%) with placebo	RR 0.87 95% CI 0.61 to 1.25	⟷	Not significant
[27] RCT	1356 women between 14 to 22 weeks' gestation	**Pre-eclampsia** 164/681 (24%) with vitamin C (1000 mg/day) plus vitamin E (400 IU/day) 157/674 (23%) with placebo	RR 1.0 95% CI 0.9 to 1.3	⟷	Not significant

Preterm birth

Compared with placebo/no antioxidant Antioxidants seem no more effective at reducing preterm births (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[22] Systematic review	4860 women 4 RCTs in this analysis	**Preterm birth** 19.5% with vitamins C and E 18.0% with placebo Absolute results reported graphically	RR 1.07 95% CI 0.96 to 1.20	⟷	Not significant
[21] Systematic review	5198 women 5 RCTs in this analysis	**Birth before 37 weeks** 540/2597 (21%) with antioxidants 490/2601 (19%) with placebo	RR 1.10 95% CI 0.99 to 1.22	⟷	Not significant

No data from the following reference on this outcome. [23] [24] [25] [26] [27]

Seizures

No data from the following reference on this outcome. [21] [22] [23] [24] [25] [26] [27]

Need for further interventions

No data from the following reference on this outcome. [21] [22] [23] [24] [25] [26] [27]

Use of resources

No data from the following reference on this outcome. [21] [22] [23] [24] [25] [26] [27]

Child development

No data from the following reference on this outcome. [21] [22] [23] [24] [25] [26] [27]

Adverse effects

No data from the following reference on this outcome. [21] [22] [23] [24] [25] [26] [27]

Further information on studies

[21] The largest trial (5021 women) in the first systematic review was quasi-randomised, and only three of the 7 included trials were rated as high quality. There are insufficient data for reliable conclusions about the effects on other substantive outcomes, such as perinatal death.

Comment: None.

OPTION MARINE OIL (FISH OIL) AND OTHER PROSTAGLANDIN PRECURSORS (EVENING PRIMROSE OIL)

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether fish oil is beneficial in high-risk women because there are insufficient data to draw reliable conclusions.

Benefits and harms

Marine oil versus placebo or no treatment:

We found three systematic reviews. [28] [29] [30] The first review (search date 2005, 6 RCTs, 2783 women; see further information on studies below) compared marine oil and other prostaglandin precursors versus placebo or no treatment

for the prevention of pre-eclampsia. [28] The second systematic review (search date 2005, 6 RCTs, 1278 women), which was restricted to women with a low-risk pregnancy and included three RCTs of oil from non-marine sources, reached similar conclusions to the first review. [29] The third review (search date 2006, 4 RCTs, 1264 women), which was restricted to women with a high-risk pregnancy, also reached similar conclusions. [30] Therefore, only data from the first review are reported here.

Morbidity

Compared with placebo or no treatment Marine oil seems no more effective at increasing birth weight (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infant morbidity					
[28] Systematic review	2440 women 3 RCTs in this analysis	**Birth weight** with marine oil with placebo or no treatment Absolute results not reported	WMD 47 g 95% CI 1 g to 93 g	○○○	marine oil

Development of pre-eclampsia

Compared with placebo or no treatment Marine oil seems no more effective at reducing the risk of pre-eclampsia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[28] Systematic review	1683 women 4 RCTs in this analysis	**Pre-eclampsia** 42/827 (5%) with marine oil 51/856 (6%) with placebo or no treatment	RR 0.86 95% CI 0.59 to 1.27	⟷	Not significant

Preterm birth

Compared with placebo or no treatment Marine oil seems no more effective at reducing preterm birth, or increasing the gestation period (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[28] Systematic review	1916 women 5 RCTs in this analysis	**Preterm birth** 205/947 (22%) with marine oil 228/969 (24%) with placebo or no treatment	RR 0.92 95% CI 0.79 to 1.07	⟷	Not significant
[28] Systematic review	1621 women 3 RCTs in this analysis	**Length of gestation** with marine oil with placebo or no treatment Absolute results not reported Mean 2.6 days longer with marine oil	WMD 2.55 days 95% CI 1.03 days to 4.07 days	○○○	marine oil

Mortality

No data from the following reference on this outcome. [28]

Seizures

No data from the following reference on this outcome. [28]

Need for further interventions

No data from the following reference on this outcome. [28]

Use of resources

No data from the following reference on this outcome. [28]

Child development

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] Systematic review	1386 women 3 RCTs in this analysis	**Belching** 320/762 (42%) with marine oil 64/624 (10%) with placebo or no treatment	RR 3.55 95% CI 2.78 to 4.52	●●○	placebo or no treatment
[28] Systematic review	1354 women 3 RCTs in this analysis	**Unpleasant taste** 193/743 (26%) with marine oil 22/611 (4%) with placebo or no marine oil	RR 6.17 95% CI 4.03 to 9.44	●●●	placebo or no treatment
[28] Systematic review	Number of women unclear	**Maternal adverse effects** with marine oil with placebo or no marine oil Absolute results not reported	The review found no significant difference between groups in nausea, vomiting, stomach pain, diarrhoea, or constipation. It also found no significant difference between groups in any bleeding complications such as nasal bleeding, antepartum vaginal bleeding, maternal anaemia, vaginal blood loss after birth, and blood loss at birth	⟷	Not significant

Further information on studies

[28] In the review, of the 6 included RCTs, 4 RCTs used oil derived from the body of a fish, the fifth RCT used a combination of evening primrose oil and fish (body) oil, while the sixth RCT assessed the consumption of eggs enriched with docosahexaenoic acid (DHA) by feeding laying hens with algal (marine) oil. RCTs of fish oil may have been difficult to blind because of the distinctive taste of fish oil. One RCT found that olive oil provided better masking than a non-oil placebo. [31]

[28] The review included all pregnant women, regardless of their risk for pre-eclampsia, preterm birth, or intrauterine growth retardation, and excluded women with established pre-eclampsia or suspected intrauterine growth retardation.

Comment: None.

OPTION GLYCERYL TRINITRATE

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether glyceryl trinitrate is beneficial in high-risk women because there are insufficient data to draw reliable conclusions.

Benefits and harms

Glyceryl trinitrate versus placebo:

We found one systematic review (search date 2006, 6 RCTs, 310 women) comparing nitric oxide donors (glyceryl trinitrate [GTN]) or precursors (L-arginine) with either placebo or no nitric oxide. [32]

Development of pre-eclampsia

Compared with placebo/no treatment Glyceryl trinitrate seems no more effective at reducing the risk of pre-eclampsia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[32] Systematic review	124 women 3 RCTs in this analysis	**Pre-eclampsia** 18/66 (27%) with glyceryl trinitrate or L-arginine 14/58 (24%) with placebo	RR 1.12 95% CI 0.61 to 2.08 P = 0.71	⟷	Not significant

Mortality

No data from the following reference on this outcome. [32]

Morbidity

No data from the following reference on this outcome. [32]

Seizures

No data from the following reference on this outcome. [32]

Preterm birth

No data from the following reference on this outcome. [32]

Need for further interventions

No data from the following reference on this outcome. [32]

Use of resources

No data from the following reference on this outcome. [32]

Child development

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] Systematic review	56 women 2 RCTs in this analysis	**Headache** 9/28 (32%) with glyceryl trinitrate or L-arginine 1/28 (4%) with placebo	RR 6.85 95% CI 1.42 to 33.04	●●●	placebo
[32] Systematic review	56 women 2 RCTs in this analysis	**Skin rash in mother** 4/28 (14%) with glyceryl trinitrate or L-arginine 6/28 (21%) with placebo	RR 0.68 95% CI 0.22 to 2.07	⟷	Not significant

Further information on studies

[32] The systematic review also compared nitric oxide with antiplatelet drugs (1 RCT, 76 women); there were insufficient data to draw any reliable conclusions.

Comment: None.

OPTION MAGNESIUM SUPPLEMENTATION

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .

- We don't know whether magnesium supplementation is beneficial in high-risk women because there are insufficient data to draw reliable conclusions.

Benefits and harms

Magnesium supplementation versus placebo:

We found one systematic review (search date 2001, 2 RCTs, 474 women) comparing magnesium supplements versus placebo. [33]

Development of pre-eclampsia

Compared with placebo Magnesium supplements seem no more effective at reducing the risk of pre-eclampsia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[33] Systematic review	474 women 2 RCTs in this analysis	**Pre-eclampsia** 34/235 (15%) with magnesium supplements 40/239 (17%) with placebo	RR 0.87 95% CI 0.57 to 1.32	⟷	Not significant

Mortality

No data from the following reference on this outcome. [33]

Morbidity

No data from the following reference on this outcome. [33]

Seizures

No data from the following reference on this outcome. [33]

Preterm birth

No data from the following reference on this outcome. [33]

Need for further interventions

No data from the following reference on this outcome. [33]

Use of resources

No data from the following reference on this outcome. [33]

Child development

No data from the following reference on this outcome. [33]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] Systematic review	Number of women unclear	**Gastrointestinal adverse effects in mother** with magnesium supplements with placebo Absolute results not reported	RR 0.89 95% CI 0.75 to 1.05	⟷	Not significant

Further information on studies

[33] This review included 7 trials with 2689 women, of which only two (474 women) reported data for pre-eclampsia. There is, therefore, also a possibility of bias in that 5 trials did not report this outcome.

Comment: None.

OPTION SALT RESTRICTION

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether salt restriction is beneficial in high-risk women because there are insufficient data to draw reliable conclusions.

Benefits and harms

Salt restriction versus normal dietary intake:

We found one systematic review (search date 2005, 2 RCTs, 603 women) comparing reduced salt with normal dietary salt intake. [34]

Development of pre-eclampsia

Compared with normal dietary intake A low-salt diet seems no more effective at reducing the risk of pre-eclampsia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[34] Systematic review	603 women 2 RCTs in this analysis	**Pre-eclampsia** with salt restriction with normal dietary intake Absolute results not reported	RR 1.11 95% CI 0.46 to 2.66	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Salt restriction involved advice to restrict dietary salt intake to 20 to 50 mmol/day			

Mortality

No data from the following reference on this outcome. [34]

Morbidity

No data from the following reference on this outcome. [34]

Seizures

No data from the following reference on this outcome. [34]

Preterm birth

No data from the following reference on this outcome. [34]

Need for further interventions

No data from the following reference on this outcome. [34]

Use of resources

No data from the following reference on this outcome. [34]

Child development

No data from the following reference on this outcome. [34]

Adverse effects

No data from the following reference on this outcome. [34]

Further information on studies

[34] The trials of salt restriction were conducted in the Netherlands, where advice to restrict salt intake during pregnancy has been routine for many years. Such advice is no longer widespread elsewhere.

Comment: None.

OPTION ATENOLOL

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether atenolol reduces the risk of pre-eclampsia, but it may worsen outcomes for babies.

Benefits and harms

Atenolol versus placebo:

We found one small RCT comparing atenolol versus placebo. [35]

Morbidity

Compared with placebo Atenolol may be less effective at increasing the birth weight of babies born to women without hypertension but with a cardiac output of >7.4 L/minute (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Birth weight					
[35] RCT	Primiparous women, number not reported Subgroup analysis	**Mean birth weight** with atenolol (100 mg/day) with placebo Absolute results not reported	Mean difference 440 g P = 0.02	○○○	placebo

No data from the following reference on this outcome. [35]

Development of pre-eclampsia

Compared with placebo Atenolol seems no more effective at reducing the risk of pre-eclampsia in women without hypertension but with a cardiac output of >7.4 L/minute (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[35] RCT	68 women without hypertension selected because they had a cardiac output of >7.4 L/minute	**Pre-eclampsia** 1/28 (4%) with atenolol (100 mg daily) 5/28 (18%) with placebo	RR 0.20 95% CI 0.02 to 1.60 This trial was too small for reliable estimates of clinically important effects on substantive outcomes	⟷	Not significant

Mortality

No data from the following reference on this outcome. [35]

Seizures

No data from the following reference on this outcome. [35]

Preterm birth

No data from the following reference on this outcome. [35]

Need for further interventions

No data from the following reference on this outcome. [35]

Use of resources

No data from the following reference on this outcome. [35]

Child development

No data from the following reference on this outcome. [35]

Adverse effects

No data from the following reference on this outcome. [35]

Further information on studies

Comment: Although the possible benefits of atenolol for prevention of pre-eclampsia remain unclear, the reduction in birth weight may be real. Concerns about the possible harmful effects of atenolol on fetal growth and development have been discussed for some time (see harms of antihypertensive agents, p 23). [36] [37]

QUESTION **What are the effects of interventions in women who develop mild to moderate hypertension during pregnancy?**

OPTION **ANTIHYPERTENSIVE AGENTS**

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .

- For women with mild to moderate hypertension during pregnancy, antihypertensive drugs reduce the risk of progression to severe hypertension, but may not improve other clinical outcomes.
- ACE inhibitors have been associated with fetal renal failure, and beta-blockers are associated with the baby being born small for its gestational age.

Benefits and harms

Antihypertensive drugs versus placebo/no antihypertensive drugs:

We found two systematic reviews. [38] [39] The first systematic review (search date 2006, 46 RCTs, 4282 women with mild to moderate hypertension) included trials that compared any antihypertensive drug versus placebo or versus another antihypertensive drug. [38] The second systematic review (search date 2004, 29 RCTs, 2500 women with mild to moderate hypertension) included only studies that compared beta-blockers versus no antihypertensive drug or versus another antihypertensive drug. [39]

Mortality

Compared with placebo/no antihypertensive drug We don't know whether antihypertensive drugs are more effective at reducing fetal or neonatal deaths (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fetal or neonatal death					
[38] Systematic review	3081 women with mild to moderate hypertension 26 RCTs in this analysis	**Fetal or neonatal death** with antihypertensive drug with no antihypertenisive drug Absolute results not reported	RR 0.73 95% CI 0.50 to 1.08	⟷	Not significant

No data from the following reference on this outcome. [39]

Morbidity

Compared with no beta-blockers Beta-blockers seem more effective at reducing the proportion of babies born small for their gestational age to women with mild to moderate hypertension (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Babies born small for gestational age					
[39] Systematic review	854 women with mild to moderate hypertension 13 RCTs in this analysis	**Baby's risk of being small for its gestational age** with beta-blockers with no beta-blockers Absolute results not reported	RR 1.34 95% CI 1.01 to 1.79	●●○	no beta-blockers

No data from the following reference on this outcome. [38]

Development of pre-eclampsia

Compared with placebo/no antihypertensive drug Antihypertensive drugs may be more effective at reducing the risk of severe hypertension, but not of pre-eclampsia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of severe hypertension or pre-eclampsia					
[38] Systematic review	2409 women with mild to moderate hypertension 19 RCTs in this analysis	**Severe hypertension** with antihypertensive drug with no anithypertensive drug Absolute results not reported	RR 0.50 95% CI 0.41 to 0.61 NNT 10 95% CI 8 to 13	●○○	antihypertensive drugs

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] Systematic review	2702 women with mild to moderate hypertension 22 RCTs in this analysis	**Pre-eclampsia** with antihypertensive drug with no antihypertensive drug Absolute results not reported	RR 0.97 95% CI 0.83 to 1.13	⟷	Not significant
[39] Systematic review	1128 women with mild to moderate hypertension 11 RCTs in this analysis	**Severe hypertension** with beta-blockers with no beta-blockers Absolute results not reported	RR 0.37 95% CI 0.26 to 0.53	●●○	beta-blockers

Seizures

No data from the following reference on this outcome. [38] [39]

Preterm birth

No data from the following reference on this outcome. [38] [39]

Need for further interventions

No data from the following reference on this outcome. [38] [39]

Use of resources

No data from the following reference on this outcome. [38] [39]

Child development

No data from the following reference on this outcome. [38] [39]

Adverse effects

No data from the following reference on this outcome. [38] [39]

Antihypertensive drugs versus each other:

We found one systematic review (search date 2006, 46 RCTs, 4282 women with mild to moderate hypertension), which included studies that compared any antihypertensive drug versus placebo or versus another antihypertensive drug. [38]

Development of pre-eclampsia

Compared with methyldopa Beta-blockers seem more effective at reducing the risk of severe hypertension in women with mild to moderate hypertension (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[38] Systematic review	493 women with mild to moderate hypertension 8 RCTs in this analysis	**Severe hypertension** with beta-blockers with methyldopa Absolute results not reported	RR 0.79 95% CI 0.63 to 0.99	●○○	beta-blockers

Mortality

No data from the following reference on this outcome. [38]

Morbidity

No data from the following reference on this outcome. [38]

Seizures

No data from the following reference on this outcome. [38]

Preterm birth

No data from the following reference on this outcome. [38]

Use of resources

No data from the following reference on this outcome. [38]

Need for further interventions

No data from the following reference on this outcome. [38]

Child development

No data from the following reference on this outcome. [38]

Adverse effects

No data from the following reference on this outcome. [38]

Further information on studies

[38] [39] Neither systematic review found any clear difference among any of these drugs for the risk of developing severe hypertension or pre-eclampsia. **Adverse effects:** The antihypertensive agents included in the systematic reviews seem to have been well tolerated during pregnancy, but adverse effects were not reported in many RCTs. All antihypertensive drugs cross the placenta, but few trials reported possible adverse effects for the baby.

Comment:

One systematic review (search date 1999, 13 small RCTs in women with pre-existing chronic hypertension) found that the effects of antihypertensive agents in women with pre-existing chronic hypertension were similar to those described above for women with pregnancy-induced hypertension. [40] The review did not establish or exclude benefit from treatment. It found that ACE inhibitors used in the second or third trimester were associated with fetal renal failure.

Meta-regression analysis within within one systematic review suggested that lowering blood pressure for women with mild or moderate hypertension may increase the risk of having a baby small for its gestational age. [40]

We found one study in Russian that is awaiting translation and will be included in future updates, if relevant. [41]

Clinical guide:
The RCTs were too small to exclude beneficial effects of antihypertensive agents. The trials had problems with methods. Many were not placebo-controlled, and few attempted to blind blood pressure measurement. Many important outcomes were reported by only a few studies. We found little evidence about adherence to treatment. Fetal exposure to ACE inhibitors during the first trimester is associated with major congenital malformations. [42] If women who are using ACE inhibitors are contemplating pregnancy, it would seem advisable to switch them to another drug well in advance of conception.

OPTION BED REST/HOSPITAL ADMISSION

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether bed rest or hospital admission are beneficial in women who develop mild to moderate hypertension during pregnancy.

Benefits and harms

Bed rest/hospital admission versus no hospital admission:

We found one systematic review (search date 2005, 4 RCTs, 449 women) comparing some rest in hospital with normal activity at home for women with non-proteinuric hypertension. [43]

Development of pre-eclampsia

Compared with no hospital admission We don't know whether some rest in hospital is more effective than normal activity at home at reducing the incidence of severe hypertension in women with non-proteinuric hypertension (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of severe hypertension or pre-eclampsia					
[43] Systematic review	218 women Data from 1 RCT	**Severe hypertension** 25/110 (23%) with rest in hospital 42/108 (39%) with normal activity at home	RR 0.58 95% CI 0.38 to 0.89	●○○	rest in hospital

Preterm birth

Compared with no hospital admission Some rest in hospital seems modestly more effective at lowering the risk of preterm birth in women with non-proteinuric hypertension (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[43] Systematic review	218 women Data from 1 RCT	**Preterm birth** 13/110 (12%) with rest in hospital 24/108 (22%) with normal activity at home	RR 0.53 95% CI 0.29 to 0.99	●○○	rest in hospital

Mortality

No data from the following reference on this outcome. [43]

Morbidity

No data from the following reference on this outcome. [43]

Seizures

No data from the following reference on this outcome. [43]

Need for further interventions

No data from the following reference on this outcome. [43]

Use of resources

No data from the following reference on this outcome. [43]

Child development

No data from the following reference on this outcome. [43]

Adverse effects

No data from the following reference on this outcome. [43]

Bed rest/hospital admission versus day care:

We found one systematic review (search date 2009, 3 RCT, 504 women), which compared hospital admission versus antenatal day care units. [44]

Development of pre-eclampsia

Compared with day care Inpatient care is no more effective at reducing maternal blood pressure (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[44] Systematic review	395 women Data from 1 RCT	**Maternal blood pressure** 77/132 (58%) with inpatient care 150/263 (57%) with day care	RR 0.98 95% CI 0.82 to 1.17 P = 0.80	⟷	Not significant

Use of resources

Compared with day care Antenatal day care seems more effective at reducing the number of antenatal hospital admissions compared with inpatient care (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Antenatal hospital admission					
[44] Systematic review	109 women 2 RCTs in this analysis	**Proportion of women admitted to hospital antenally** 47/50 (94%) with antenatal day care units 25/59 (42%) with inpatient care	RR 0.46 95% CI 0.34 to 0.62	●●○	antenatal day care units

Mortality

No data from the following reference on this outcome. [44]

Morbidity

No data from the following reference on this outcome. [44]

Seizures

No data from the following reference on this outcome. [44]

Preterm birth

No data from the following reference on this outcome. [44]

Need for further interventions

No data from the following reference on this outcome. [44]

Child development

No data from the following reference on this outcome. [44]

Adverse effects

No data from the following reference on this outcome. [44]

Further information on studies

[43] The reduction in severe hypertension for women allocated rest in hospital rather than routine activity at home should be interpreted with caution, as this may reflect "white-coat" hypertension, ascertainment bias, or both, in that women at home had only weekly assessment of their blood pressure. The review found that significantly more women preferred being at home than hospital admission (RR 3.00, 95% CI 1.43 to 6.31). The review also compared bed rest in hospital with normal ambulation in hospital for women with proteinuric hypertension (2 RCTs, 145 women), but the RCTs were too small for any reliable conclusions to be drawn.

Comment: **Clinical guide:**
It has been suggested that hospital admission increases the risk of venous stasis, thromboembolic disease, or infection, but we found no evidence in this context. Trials of hospital admission and bed rest in hospital were largely conducted before widespread introduction of day care assessment units. Women with hypertension during pregnancy are now often seen in day care units, but only one small RCT has compared day care assessment versus assessment in an outpatient clinic. In the systematic review of day care, women preferred not to be admitted to hospital, and were less satisfied with their care 4 days after the birth if they had been allocated routine care.

QUESTION What are the effects of interventions in women who develop severe pre-eclampsia or very high blood pressure during pregnancy?

OPTION PROPHYLACTIC ANTICONVULSANTS FOR WOMEN WITH SEVERE PRE-ECLAMPSIA

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- Magnesium sulphate reduces the risk of first or subsequent seizures in women with severe pre-eclampsia compared with placebo.

Benefits and harms

Prophylactic magnesium versus placebo/no anticonvulsant:

We found two systematic reviews (search date 2002, 13 RCTs, 15,558 women; [45] search date 2008, 5 RCTs, 6145 babies [46]) and three long-term follow-up reports of an RCT [47] included in the first review. [45] Follow up of the RCT assessed long-term results in both women and children. [48] [49]

Mortality

Compared with placebo/no anticonvulsants Prophylactic magnesium sulphate is no more effective at reducing stillbirths, maternal mortality, neonatal mortality, or neurosensory disability or mortality in children at 18 months (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal mortality					
[45] Systematic review	10,795 women 2 RCTs in this analysis	**Maternal mortality** 11/5400 (0.2%) with magnesium sulphate 21/5395 (0.4%) with placebo	RR 0.54 95% CI 0.26 to 1.10	⟷	Not significant
[48] Systematic review	3375 women with 2-year old children Further report of reference [47]	**Risk of maternal death or serious morbidity , 2 years after the birth of their children** 58/1650 (3.5%) with magnesium sulphate 72/1725 (4.2%) with placebo	RR 0.84 95% CI 0.60 to 1.18 Of those women selected for follow-up (4782 of 7927 women randomised at centres participating in the follow-up study), the results were based on 3375/4782 (71%) women who responded	⟷	Not significant
Infant mortality or neurodisability					
[46] Systematic review	6145 preterm children 5 RCTs in this analysis	**Death or cerebral palsy** 547/3052 (18%) with magnesium sulphate 583/3093 (19%) with placebo	RR 0.94 95% CI 0.78 to 1.12 P = 0.48	⟷	Not significant
[49] Systematic review	3283 children aged 18 months old Further report of reference [47]	**Death or neurosensory disability , 18 months** 245/1635 (15%) with magnesium sulphate 233/1648 (14%) with placebo	RR 1.06 95% CI 0.90 to 1.25 Of those children selected for follow-up (4483 of 6922 children of women randomised before delivery at centres participating in the follow-up study), the results were based on 3283/4483 (73%) children for whom data were available	⟷	Not significant
[45] Systematic review	9961 women randomised before delivery 3 RCTs in this analysis	**Still birth or neonatal death** 634/5003 (13%) with magnesium sulphate 611/4958 (12%) with placebo	RR 1.04 95% CI 0.93 to 1.15	⟷	Not significant

Seizures

Compared with placebo/no anticonvulsants Prophylactic magnesium sulphate is more effective at reducing the risk of eclampsia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[45] Systematic review	11,444 women 6 RCTs in this analysis	**Eclampsia** 43/5722 (1%) with magnesium sulphate 107/5722 (2%) with placebo	RR 0.41 95% CI 0.29 to 0.58 NNT 100 95% CI 50 to 100	●●○	magnesium sulphate

No data from the following reference on this outcome. [46]

Child development

Compared with placebo/no anticonvulsants Prophylactic magnesium sulphate seems more effective at reducing the risk of cerebral palsy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Child development					
[46] Systematic review	6145 preterm children 5 RCTs in this analysis	**Cerebral palsy** 104/3052 (3%) with magnesium sulphate 154/3093 (5%) with placebo	RR 0.68 95% CI 0.54 to 0.87 P = 0.002	●○○	magnesium sulphate

Need for further interventions

Compared with placebo/no anticonvulsants Magnesium sulphate increases the need for a caesarean section (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Caesarean section					
[45] Systematic review	10,108 women	**Caesarean section** 2528/5082 (50%) with magnesium sulphate 2370/5026 (47%) with placebo	RR 1.05 95% CI 1.01 to 1.10 NNH 34 95% CI 25 to 100	●○○	placebo

No data from the following reference on this outcome. [46]

Use of resources

No data from the following reference on this outcome. [46]

Adverse effects

Compared with placebo/no anticonvulsants Magnesium sulphate seems less effective at reducing adverse effects, such as flushing and respiratory depression (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] RCT	9992 women	**Maternal adverse effects** 1201/4999 (24%) with magnesium sulphate	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		228/4993 (5%) with placebo			
[45] Systematic review	10,127 women 2 RCTs in this analysis	**Flushing** 1032/5066 (20%) with magnesium sulphate 110/5061 (2%) with placebo	P value not reported		
[45] Systematic review	10,677 women 2 RCTs in this analysis	**Maternal respiratory depression** 52/5344 (1.0%) with magnesium sulphate 26/5333 (0.5%) with placebo	RR 1.98 95% CI 1.24 to 3.15	●○○	placebo

No data from the following reference on this outcome. [46]

Morbidity

No data from the following reference on this outcome. [45] [46]

Development of pre-eclampsia

No data from the following reference on this outcome. [45] [46]

Preterm birth

No data from the following reference on this outcome. [45] [46]

Prophylactic magnesium sulphate versus phenytoin, nimodipine, or diazepam:

We found one systematic review (search date 2002, 13 RCTs, 15,558 women) [45] and one small subsequent RCT. [50]

Seizures

Compared with phenytoin, nimodipine, or diazepam Magnesium sulphate is more effective than phenytoin and nimodipine at reducing the risk of eclampsia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[45] Systematic review	2241 women 2 RCTs in this analysis	**Eclampsia** 0/1109 (0%) with magnesium sulphate 10/1132 (0.8%) with phenytoin	RR 0.05 95% CI 0 to 0.84	●●●	magnesium sulphate
[45] Systematic review	1650 women Data from 1 RCT	**Eclampsia** 7/831 (1%) with magnesium sulphate	RR 0.33 95% CI 0.14 to 0.77	●●○	magnesium sulphate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		21/819 (3%) with nimodipine			
[50] RCT	50 women	**Eclampsia** 0/25 (0%) with magnesium sulphate 2/25 (8%) with phenytoin	P = 0.24	⟷	Not significant

Need for further interventions

Compared with phenytoin Magnesium sulphate seems less effective at reducing the need for caesarean section (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Caesarean section					
[45] Systematic review	Number of women unclear	**Caesarean section** with magnesium sulphate with phenytoin Absolute results not reported	RR 1.21 95% CI 1.05 to 1.41 NNH 21 95% CI 12 to 83	●○○	phenytoin

No data from the following reference on this outcome. [45] [50]

Mortality

No data from the following reference on this outcome. [45] [50]

Morbidity

No data from the following reference on this outcome. [45] [50]

Development of pre-eclampsia

No data from the following reference on this outcome. [45] [50]

Preterm birth

No data from the following reference on this outcome. [45] [50]

Use of resources

No data from the following reference on this outcome. [45] [50]

Child development

No data from the following reference on this outcome. [45] [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	1650 women	**Maternal respiratory problems** 11/831 (1.3%) with magnesium sulphate 3/819 (0.4%) with nimodipine	RR 3.61 95% CI 1.01 to 12.91	●●○	nimodipine

No data from the following reference on this outcome. [50]

Further information on studies

[45] There was insufficient evidence for reliable conclusions about magnesium sulphate compared with diazepam (2 RCTs, 66 women).

[48] [49] Most of the data in these trials refer to women with relatively severe pre-eclampsia. One small study recruited only women with mild pre-eclampsia. Long-term follow-up of women and children in one large RCT is reassuring, in that the lower risk of eclampsia is not associated with any clear difference in longer-term outcome for the women or children. A subgrooup analysis from this trail of 774 women and their 827 children followed up in the UK supported the main findings reported above; there were also no clear differences in the child's behaviour, women's fertility, or use of health service resources. [51]

Comment: Weak evidence from two case-control studies suggested that magnesium sulphate may be associated with a decreased risk of cerebral palsy in babies weighing <1500 g. [52] [53] This hypothesis has been tested in a large RCT. [54] The RCT found that magnesium sulphate was associated with a non-significant reduction in the composite outcome of death or cerebral palsy compared with placebo (123/629 [20%] with magnesium sulphate *v* 149/626 [24%] with placebo; RR 0.83, 95% CI 0.66 to 1.03). [54] One small RCT evaluated magnesium sulphate for preventing and treating preterm labour in women who did not have pre-eclampsia. It found an increase in infant mortality for babies born to these women. Many of the infants had low birth weight (<1500 g). [55]

OPTION ANTIHYPERTENSIVE DRUGS FOR VERY HIGH BLOOD PRESSURE

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- There is consensus that women who develop severe hypertension in pregnancy should receive antihypertensive treatment, but we don't know which antihypertensive agent is most effective.

Benefits and harms

Antiypertensive drugs versus each other:

We found one systematic review (search date 2006, 24 RCTs, 2949 women [56]) and 4 subsequent RCTs. [57] [58] [59] [60] The review compared many antihypertensive drugs (such as labetalol, nifedipine, methyldopa, diazoxide, urapidil, magnesium sulphate, prazosin, nimodipine, and ketanserin) mainly versus hydralazine. [56]

Seizures

Different antihypertensive drugs compared with each other We don't know whether one antihypertensive drug (such as hydralazine, labetalol, nifedipine, nitroglycerine, methyldopa, diazoxide, urapidil, magnesium sulphate, prazosin, nimodipine, or ketanserin) is more effective than the others at reducing blood pressure (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[56] Systematic review	263 women 5 RCTs in this analysis	**Persistent high blood pressure** 8/135 (6%) with calcium channel blockers 23/128 (18%) with hydralazine	RR 0.33 95% CI 0.15 to 0.70	●●○	calcium channel blockers
[56] Systematic review	1650 women Data from 1 RCT	**Persistent high blood pressure** 374/819 (47%) with nimodipine 451/831 (54%) with magnesium sulphate	RR 0.84 95% CI 0.76 to 0.93	●○○	nimodipine
[56] Systematic review	1683 women 2 RCTs in this analysis	**Eclampsia** 21/837 (3%) with nimodipine 9/846 (1%) with magnesium sulphate	RR 2.24 95% CI 1.06 to 4.73	●●○	magnesium sulphate
[57] RCT	200 women	**Persistent hypertension** with labetalol with hydralazine Absolute results not reported Both interventions were repeated after 20 minutes if needed	Reported as not significant P value not reported	⟷	Not significant
[56] Systematic review	180 women 3 RCTs in this analysis	**Persistent hypertension** 26/96 (27%) with ketanserin 5/84 (6%) with hydralazine	RR 4.79 95% CI 1.95 to 11.73	●●○	hydralazine
[59] RCT	32 women	**Mean change in arterial blood pressure , 1 hour** –29 ± 5 mmHg with intravenous nitroglycerine –24 ± 6 mmHg with sublingual nifedipine All women received a loading dose of magnesium sulphate before group allocation	P = 0.04	○○○	nitroglycerine
[60] RCT	124 women	**Target blood pressure** 27/63 (43%) with intravenous hydralazine 41/61 (67%) with mini-bolus diazoxide	RR 0.63 95% CI 0.45 to 0.89 P = 0.01	●○○	diazoxide

No data from the following reference on this outcome. [58]

Mortality

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Morbidity

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Development of pre-eclampsia

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Need for further interventions

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Use of resources

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Child development

No data from the following reference on this outcome. [56] [57] [58] [59] [60]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] Systematic review	1650 women Data from 1 RCT	**Maternal respiratory difficulties** 3/819 (0.4%) with nimodipine 11/831 (1.3%) with magnesium sulphate	RR 0.28 95% CI 0.08 to 0.99	●●○	nimodipine
[56] Systematic review	1650 women Data from 1 RCT	**Postpartum haemorrhage** 8/819 (1%) with nimodipine 20/831 (2%) with magnesium sulphate	RR 0.41 95% CI 0.18 to 0.92	●●○	nimodipine
[56] Systematic review	90 women Data from 1 RCT	**Hypotension** with labetalol with diazoxide Absolute results not reported Hypotension may compromise fetoplacental blood flow	RR 0.06 95% CI 0 to 0.99	●●●	labetalol
[56] Systematic review	1650 women Data from 1 RCT	**Flushing** 13/819 (2%) with nimodipine	RR 0.22 95% CI 0.12 to 0.40	●●○	nimodipine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		59/831 (7%) with magnesium sulphate			
[56] Systematic review	1650 women Data from 1 RCT	**Maternal adverse effects** with nimodipine with magnesium sulphate Absolute results not reported	The review found no significant difference between groups in the risk of headache, or nausea and vomiting	⟷	Not significant
[56] Systematic review	120 women 3 RCTs in this analysis	**Maternal adverse effects** 13/64 (20%) with ketanserin 36/56 (64%) with hydralazine	RR 0.32 95% CI 0.19 to 0.53	●●○	ketanserin
[58] RCT	42 women	**Hypotension , 6 hours** with intravenous urapidil with hydralazine Absolute results not reported	Reported as not significant No P value reported	⟷	Not significant
[57] RCT	200 women	**Hypotension** with labetalol with hydralazine Absolute results not reported Both interventions were repeated after 20 minutes if needed	Reported as not significant P value not reported	⟷	Not significant
[60] RCT	124 women	**Hypotension** 24/63 (38%) with hydralazine 10/61 (16%) with diazoxide	P <0.01	○○○	diazoxide

No data from the following reference on this outcome. [59]

Further information on studies

[56] Overall, there was no clear evidence that one drug in the review was better than another.

Comment: There is consensus that women with severe hypertension during pregnancy should have antihypertensive treatment. Placebo-controlled trials would therefore be unethical. Women in these studies had blood pressures high enough to merit immediate treatment, and many also had proteinuria or "severe pre-eclampsia". The trials were small and reported few outcomes other than control of blood pressure. In most trials, there was no blinding after trial entry.

OPTION ANTIOXIDANTS

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We found no direct information from RCTs about antioxidants in women with severe pre-ecampsia.

Benefits and harms

Antioxidants versus placebo:

We found no systematic review. We found one RCT (56 women with severe pre-eclampsia at 24–32 weeks' gestation) comparing vitamin E plus vitamin C plus allopurinol versus placebo. It was too small for reliable conclusions to be drawn.

Further information on studies

Comment: None.

OPTION CHOICE OF ANALGESIA DURING LABOUR

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We found no RCTs about analgesia in women with severe pre-eclampsia that assessed mortality, morbidity, or rates of pre-eclampsia.

Benefits and harms

Epidural analgesia versus patient-controlled intravenous analgesia:

We found two RCTs. [61] [62] When assessing potential benefits of the alternative analgesia strategies, the RCTs only assessed the outcome of pain; see further information on studies. See below for comparative adverse effects of epidural versus patient-controlled intravenous analgesia.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[61] RCT	116 women	**Hypotension** 5/56 (9%) with epidural analgesia 0/60 (0%) with intravenous (iv) analgesia	Reported as not significant No P value reported The number of events was too small to draw reliable conclusions	⟷	Not significant
[61] RCT	116 women	**Need for neonatal naloxone** 5/56 (9%) with epidural analgesia 31/60 (52%) with iv analgesia	RR 5.71 95% CI 2.39 to 13.60 NNH 3 95% CI 2 to 4	●●●	epidural analgesia
[62] RCT	738 women	**Mean duration of second stage of labour** 53 minutes with epidural analgesia 40 minutes with iv analgesia	P value not reported		
[62] RCT	738 women	**Intrapartum fever** 76/372 (20%) with epidural analgesia 26/366 (7%) with iv analgesia	RR 2.88 95% CI 1.89 to 4.38	●●○	iv analgesia
[62] RCT	738 women	**Forceps delivery** 51/372 (14%) with epidural analgesia 27/366 (7%) with iv analgesia	RR 1.86 95% CI 1.19 to 2.90	●○○	iv analgesia
[62] RCT	738 women	**Hypotension treatment** 40/372 (11%) with epidural analgesia	P <0.001	○○○	iv analgesia

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/366 (0%) with iv analgesia			
[62] RCT	738 women	**Need for neonatal naloxone** 2/372 (1%) with epidural analgesia 40/366 (12%) with iv analgesia	P value not reported		

Other forms of intrapartum analgesia versus each other:

We found no RCTs.

Further information on studies

[62] One RCT (738 women with pregnancy-induced hypertension) found that epidural analgesia reduced pain compared with iv analgesia (proportion of women reporting excellent pain relief: 54% with epidural analgesia *v* 19% with iv analgesia; P <0.001).

[61] One RCT (116 women with severe pre-eclampsia) found that epidural analgesia significantly reduced mean pain scores, but the clinical importance of the difference is unclear. The trial was too small for reliable conclusions to be drawn about other outcomes.

Comment: The drug used for patient-controlled intravenous analgesia was not reported in the first RCT. [61] Pethidine was used in the second RCT. [62]

OPTION INTERVENTIONIST CARE FOR SEVERE EARLY-ONSET PRE-ECLAMPSIA

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether early delivery improves outcomes for women with severe pre-eclampsia.

Benefits and harms

Interventionist care versus expectant management:

We found one systematic review (search date 2006, 2 RCTs, 133 women at 28–34 weeks' gestation), which compared a policy of early elective delivery by induction or caesarean section, depending on individual obstetric circumstances (interventionist management), versus a policy of delayed delivery to allow more time for fetal maturation (expectant management) in women with severe pre-eclampsia. [63] The review found insufficient evidence about effects on maternal outcomes.

Mortality

Compared with expectant management We don't know whether interventionist management is more effective at reducing stillbirths or perinatal deaths in babies born to mothers with severe early-onset pre-eclampsia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Perinatal mortality					
[63] Systematic review	133 women at 28 to 34 weeks' gestation with severe pre-eclampsia	**Death or stillbirth** with interventionist management with expectant management	RR 1.50 95% CI 0.42 to 5.41	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	2 RCTs in this analysis	Absolute results not reported			

Morbidity

Compared with expectant management Interventionist management may increase the risk of respiratory distress syndrome, necrotising enterocolitis, and rates of admission to NICUs in babies born to mothers with severe pre-eclampsia, but may be more effective at reducing the number of babies born small for gestational age (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neonatal morbidity					
[63] Systematic review	133 women at 28 to 34 weeks' gestation with severe pre-eclampsia 2 RCTs in this analysis	**Babies born small for gestational age** with interventionist management with expectant management Absolute results not reported	RR 0.36 95% CI 0.14 to 0.90	●●○	interventionist management
[63] Systematic review	133 women at 28 to 34 weeks' gestation with severe pre-eclampsia 2 RCTs in this analysis	**Respiratory distress syndrome** 34/66 (52%) with interventionist management 15/67 (22%) with expectant management	RR 2.30 95% CI 1.39 to 3.81	●●○	expectant management
[63] Systematic review	133 women at 28 to 34 weeks' gestation with severe pre-eclampsia 2 RCTs in this analysis	**Necrotising enterocolitis** with interventionist management with expectant management Absolute results not reported	RR 5.5 95% CI 1.04 to 29.56	●●●	expectant management
[63] Systematic review	133 women at 28 to 34 weeks' gestation with severe pre-eclampsia 2 RCTs in this analysis	**Rate of admission to NICU** with interventionist management with expectant management Absolute results not reported	RR 1.32 95% CI 1.13 to 1.55	●○○	expectant management

Development of pre-eclampsia

No data from the following reference on this outcome. [63]

Seizures

No data from the following reference on this outcome. [63]

Need for further interventions

No data from the following reference on this outcome. [63]

Use of resources

No data from the following reference on this outcome. [63]

Child development

No data from the following reference on this outcome. [63]

Adverse effects

No data from the following reference on this outcome. [63]

Further information on studies

Comment: None.

OPTION PLASMA VOLUME EXPANSION

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .
- We don't know whether plasma volume expansion improves outcomes for women with severe pre-eclampsia.

Benefits and harms

Plasma volume expansion versus control:

We found one systematic review (search date 2000, 3 RCTs, 61 women; [64] see further information on studies below) evaluating colloid solutions compared with placebo or no infusion, and one subsequent RCT. [65]

Mortality

Compared with control We don't know whether plasma volume expansion using colloids is more effective at reducing infant mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Perinatal mortality					
[65] RCT	216 women	**Infant mortality** 23/111 (21%) with plasma volume expansion 15/105 (14%) with no expansion	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [64]

Morbidity

Compared with control We don't know whether plasma volume expansion using colloids is more effective at reducing the proportion of women who develop haemolysis, elevated liver enzymes, and lowered platelets (HELLP) syndrome or other serious maternal morbidities (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal morbidity					
[65] RCT	216 women	**Serious maternal morbidity, including haemolysis, elevated liver enzymes** 13/111 (12%) with plasma volume expansion 11/105 (10%) with no expansion	Reported as not significant P value not reported	⟷	Not significant
[65] RCT	216 women	**Lowered platelets (HELLP) syndrome** 19/111 (17%) with plasma volume expansion 20/105 (19%) with no expansion	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [64]

Seizures

Compared with control We don't know whether plasma volume expansion using colloids is more effective at reducing the proportion of women who develop eclampsia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[65] RCT	216 women	**Eclampsia** 2/111 (1.8%) with plasma volume expansion 2/105 (1.9%) with no expansion	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [64]

Need for further interventions

Compared with placebo/no infusion Plasma volume expansion may be no more effective at reducing the need for further interventions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for further interventions					
[64] Systematic review	Number of women unclear	**Caesarean section** with plasma volume expansion with placebo/no infusion Absolute results not reported	RR 1.5 95% CI 0.8 to 2.9	⟷	Not significant
[64] Systematic review	Number of women unclear	**Need for additional treatment** with plasma volume expansion with placebo/no infusion Absolute results not reported	RR 1.5 95% CI 0.7 to 3.1	⟷	Not significant

No data from the following reference on this outcome. [65]

Development of pre-eclampsia

No data from the following reference on this outcome. [64] [65]

Preterm birth

No data from the following reference on this outcome. [64] [65]

Use of resources

No data from the following reference on this outcome. [64] [65]

Child development

No data from the following reference on this outcome. [64] [65]

Adverse effects

No data from the following reference on this outcome. [64] [65]

Further information on studies

[64] In one RCT included in the review, all women had severe pre-eclampsia. In the other two RCTs, some women did not have proteinuria at trial entry, and those with severe hypertension were excluded. These three RCTs all used a colloid rather than crystalloid solution. The systematic review found insufficient evidence to draw reliable conclusions, but suggested that plasma volume expansion is not beneficial.

[65] The subsequent RCT included women with severe early-onset pre-eclampsia, and also used a colloid solution for plasma volume expansion.

Comment: Two systematic reviews (search dates 2004 [66] and 2002 [67]) of plasma volume expansion in critically ill men and non-pregnant women have found an increased mortality with albumin (a colloid) when compared with either no expansion or expansion with crystalloid.

QUESTION **What is the best choice of anticonvulsant for women with eclampsia?**

OPTION **ANTICONVULSANTS FOR WOMEN WITH ECLAMPSIA**

- For GRADE evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension, see table, p 53 .

- Magnesium sulphate reduces the risk of subsequent seizures in women with eclampsia compared with either phenytoin or diazepam, with fewer adverse effects for the mother or baby.

Benefits and harms

Magnesium sulphate versus diazepam:

We found one systematic review (search date 2002, 7 RCTs, 1441 women). [68]

Mortality

Compared with diazepam Magnesium sulphate is more effective at reducing maternal mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[68] Systematic review	1336 women 6 RCTs in this analysis	**Maternal mortality** 26/677 (4%) with magnesium sulphate 42/659 (6%) with diazepam	RR 0.59 95% CI 0.37 to 0.94	●○○	magnesium sulphate

Morbidity

Compared with diazepam Magnesium sulphate is more effective at reducing the proportion of babies with Apgar scores <7 at 5 minutes (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neonatal morbidity					
[68] Systematic review	597 women 2 RCTs in this analysis	**Apgar scores <7 , at 5 minutes** 69/309 (22%) with magnesium sulphate 90/288 (31%) with diazepam	RR 0.72 95% CI 0.55 to 0.94	●○○	magnesium sulphate

Seizures

Compared with diazepam Magnesium sulphate is more effective at reducing further fits (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[68] Systematic review	1441 women 7 RCTs in this analysis	**Further fits** 71/737 (10%) with magnesium sulphate 162/704 (23%) with diazepam	RR 0.44 95% CI 0.34 to 0.57	●●○	magnesium sulphate

Use of resources

Compared with diazepam Magnesium sulphate is more effective at reducing the proportion of babies who stay in special care units for >7 days (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Use of resources					
[68] Systematic review	631 women 3 RCTs in this analysis	**Stay in special care baby unit of >7 days** 42/329 (13%) with magnesium sulphate 59/302 (20%) with diazepam	RR 0.66 95% CI 0.46 to 0.95	●○○	magnesium sulphate

Preterm birth

No data from the following reference on this outcome. [68]

Need for further interventions

No data from the following reference on this outcome. [68]

Child development

No data from the following reference on this outcome. [68]

Adverse effects

No data from the following reference on this outcome. [68]

Magnesium sulphate versus phenytoin:

We found one systematic review (search date 2002, 6 RCTs, 897 women), [69] one additional [70] and one subsequent RCT. [50]

Mortality

Compared with phenytoin Magnesium sulphate and phenytoin seem equally effective at reducing maternal deaths and at reducing the proportion of babies with a composite outcome of death or staying in a special care baby unit for >7 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[69] Systematic review	797 women 2 RCTs in this analysis	**Maternal death** 10/399 (3%) with magnesium sulphate 20/398 (5%) with phenytoin	RR 0.50 95% CI 0.24 to 1.05	⟷	Not significant
[69] Systematic review	643 babies Data from 1 RCT	**Composite outcome of death or staying in a special care baby unit for >7 days** with magnesium sulphate with phenytoin Absolute results not reported	RR 0.77 95% CI 0.63 to 0.95	●○○	magnesium sulphate

No data from the following reference on this outcome. [70] [50]

Morbidity

Compared with phenytoin Magnesium sulphate seems more effective at reducing pneumonia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Morbidity					
[69] Systematic review	775 women Data from 1 RCT	**Pneumonia** with magnesium sulphate with phenytoin Absolute results not reported	RR 0.44 95% CI 0.24 to 0.79	●●○	magnesium sulphate

No data from the following reference on this outcome. [70] [50]

Seizures

Compared with phenytoin Magnesium sulphate is more effective at reducing further fits (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[69] Systematic review	895 women 5 RCTs in this analysis	**Further fits** 25/448 (6%) with magnesium sulphate 83/447 (19%) with phenytoin	RR 0.31 95% CI 0.20 to 0.47	●●○	magnesium sulphate
[70] RCT	77 women	**Further fits** 20% with magnesium sulphate 36% with phenytoin Absolute numbers not reported	P < 0.05	○○○	magnesium sulphate
[50] RCT	50 women	**Further fits** 0/25 (0%) with magnesium sulphate 6/25 (24%) with phenytoin	P = 0.03	○○○	magnesium sulphate

Use of resources

Compared with phenytoin Magnesium sulphate seems more effecting at reducing the proportion of women requiring ventilation or admitted to an intensive care unit (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Use of resources					
[69] Systematic review	775 women Data from 1 RCT	**Requirement for ventilation** with magnesium sulphate with phenytoin Absolute results not reported	RR 0.66 95% CI 0.49 to 0.90	●○○	magnesium sulphate
[69] Systematic review	775 women	**Admission to ICU** with magnesium sulphate with phenytoin Absolute results not reported	RR 0.67 95% CI 0.50 to 0.89	●○○	magnesium sulphate

No data from the following reference on this outcome. [70] [50]

Preterm birth

No data from the following reference on this outcome. [70] [69] [70] [50]

Need for further interventions

No data from the following reference on this outcome. [70] [69] [70] [50]

Child development

No data from the following reference on this outcome. [70] [69] [70] [50]

Adverse effects

No data from the following reference on this outcome. [69] [70] [50]

Magnesium sulphate versus lytic cocktail:

We found one systematic review (search date 2000, 2 RCTs, 199 women) [71] and one additional RCT (199 women). [72]

Mortality

Compared with lytic cocktail Magnesium sulphate seems more effective at reducing fetal or infant deaths, but we don't know whether it is more effective at reducing maternal deaths (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[71] Systematic review	177 babies 2 RCTs in this analysis	**Fetal or infant death** 14/89 (16%) with magnesium sulphate 30/88 (34%) with lytic cocktail	RR 0.45 95% CI 0.26 to 0.79	●●○	magnesium sulphate
[71] Systematic review	198 women 2 RCTs in this analysis	**Maternal death** 1/96 (1%) with magnesium sulphate 6/102 (6%) with lytic cocktail	RR 0.25 95% CI 0.04 to 1.43	⟷	Not significant
[72] RCT	199 women	**Maternal death** 0/101 (0%) with magnesium sulphate 8/98 (8%) with lytic cocktail	P <0.005	○○○	magnesium sulphate
[72] RCT	199 women	**Perinatal death** 10% with magnesium sulphate 23% with lytic cocktail	P <0.05	○○○	magnesium sulphate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			

Morbidity

Compared with lytic cocktail Magnesium sulphate is more effective at reducing pneumonia and respiratory depression (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Morbidity					
[71] Systematic review	108 women Data from 1 RCT	**Pneumonia** 1/51 (2%) with magnesium sulphate 11/57 (19%) with lytic cocktail	RR 0.08 95% CI 0.02 to 0.42	●●●	magnesium sulphate
[71] Systematic review	198 women 2 RCTs in this analysis	**Respiratory distress** 0/96 (0%) with magnesium sulphate 8/102 (8%) with lytic cocktail	RR 0.12 95% CI 0.02 to 0.91	●●●	magnesium sulphate

No data from the following reference on this outcome. [72]

Seizures

Compared with lytic cocktail Magnesium sulphate seems more effective at reducing further fits (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Seizures					
[71] Systematic review	198 women 2 RCTs in this analysis	**Further fits** 4/96 (4%) with magnesium sulphate 49/102 (48%) with lytic cocktail	RR 0.09 95% CI 0.03 to 0.24	●●●	magnesium sulphate
[72] RCT	199 women	**Recurrence of convulsions** 2% with magnesium sulphate 62% with lytic cocktail Absolute numbers not reported	P <0.001	○○○	magnesium sulphate

Preterm birth

No data from the following reference on this outcome. [71] [72]

Need for further interventions

No data from the following reference on this outcome. [71] [72]

Use of resources

No data from the following reference on this outcome. [71] [72]

Child development

No data from the following reference on this outcome. [71] [72]

Adverse effects

No data from the following reference on this outcome. [71] [72]

Further information on studies

[68] [69] [71] The systematic reviews suggested that magnesium sulphate is safer for women — at least in the short term — than diazepam, phenytoin, or lytic cocktail. It also seemed to be safer for babies than phenytoin or lytic cocktail. We found no evidence from RCTs about longer-term adverse effects in women or children.

Comment: Most of the data came from trials that included women with antepartum or postpartum eclampsia.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Anticonvulsants for women with eclampsia New evidence added. [50] Categorisation unchanged (Beneficial).

Antihypertensive drugs for very high blood pressure New evidence added. [59] [60] Categorisation unchanged (Likely to be beneficial*).

Antioxidants (under question on the effects of preventive interventions in women at risk of pre-eclampsia) New evidence added. [21] [24] [25] [26] [27] Categorisation of antioxidants unchanged (Unknown effectiveness).

Antiplatelet drugs New evidence added. [16] Categorisation unchanged (Beneficial).

Bed rest/hospital admission New evidence added. [44] Categorisation unchanged (Unknown effectiveness).

Calcium supplementation New evidence added. [20] Categorisation unchanged (Beneficial).

Glyceryl trinitrate versus placebo/no treatment New evidence added. [32] Categorisation unchanged (Unknown effectiveness).

Marine oil (fish oil) and other prostaglandin precursors (evening primrose oil) New evidence added. [30] Categorisation unchanged (Unknown effectiveness).

Prophylactic anticonvulsants for women with severe pre-eclampsia New evidence added. [46] [50] [51] Categorisation of prophylactic magnesium sulphate in severe pre-eclampsia unchanged (Beneficial).

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Competing interests: LD is the author of studies included in this review.

Disclaimer

GRADE **Evaluation of interventions for Pre-eclampsia, eclampsia, and hypertension.**

Important outcomes	Adverse effects, Child development, Development of pre-eclampsia, Morbidity, Mortality, Need for further interventions, Preterm birth, Seizures, Use of resources								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of preventive interventions in women at risk of pre-eclampsia?									
40 (33,098) [15] [16]	Mortality	Antiplatelet drugs versus placebo	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results between reviews
36 at most (24,343) [16] [15]	Morbidity	Antiplatelet drugs versus placebo	4	0	0	0	0	High	
at least 46 (at least 32,590) [16] [15]	Development of pre-eclampsia	Antiplatelet drugs versus placebo	4	0	0	0	0	High	
29 (31,151) [15] [16]	Preterm birth	Antiplatelet drugs versus placebo	4	0	0	0	0	High	
23 (29,117) [16]	Need for further interventions	Antiplatelet drugs versus placebo	4	0	0	0	0	High	
18 (30,097) [16]	Use of resources	Antiplatelet drugs versus placebo	4	0	0	0	0	High	
11 at most (15,665 at most) [19] [20]	Mortality	Calcium supplementation versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
8 (14,359) [19]	Morbidity	Calcium supplementation versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
13 (15,730) [19] [20]	Development of pre-eclampsia	Calcium supplementation versus placebo	4	0	0	0	+1	High	Effect-size point added for RR <0.5
11 (15,275) [19] [20]	Preterm birth	Calcium supplementation versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
8 (15,234) [19] [20]	Need for further interventions	Calcium supplementation versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 6 (7239) [21] [22] [26] [27]	Mortality	Antioxidants versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (5271) [21] [22]	Morbidity	Antioxidants versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 14 (at least 8005) [21] [22] [23] [24] [25] [26] [27]	Development of pre-eclampsia	Antioxidants versus placebo	4	–1	–1	0	0	Low	Quality point deducted for methodological weaknesses. Consistency point deducted for conflicting results
5 (5198) [22] [21]	Preterm birth	Antioxidants versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (2440) [28]	Morbidity	Marine oil versus placebo or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for uncertainty about blinding
4 (1683) [28]	Development of pre-eclampsia	Marine oil versus placebo or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for uncertainty about blinding

Important outcomes	Adverse effects, Child development, Development of pre-eclampsia, Morbidity, Mortality, Need for further interventions, Preterm birth, Seizures, Use of resources								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
5 at most (1916 at most) [28]	Preterm birth	Marine oil versus placebo or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for uncertainty about blinding
3 (124) [32]	Development of pre-eclampsia	Glyceryl trinitrate versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (474) [33]	Development of pre-eclampsia	Magnesium supplementation versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for uncertainty about bias
2 (603) [34]	Development of pre-eclampsia	Salt restriction versus normal dietary intake	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (unclear) [35]	Morbidity	Atenolol versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (68) [35]	Development of pre-eclampsia	Atenolol versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of interventions in women who develop mild to moderate hypertension during pregnancy?									
26 (3081) [38]	Mortality	Antihypertensive drugs versus placebo/no antihypertensive drugs	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, methodological weaknesses, and uncertainty about adherence to treatment
13 (854) [39]	Morbidity	Antihypertensive drugs versus placebo/no antihypertensive drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting to results
at least 22 (at least 2702) [38] [39]	Development of pre-eclampsia	Antihypertensive drugs versus placebo/no antihypertensive drugs	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, methodological weaknesses, and uncertainty about adherence to treatment
8 (493) [38]	Development of pre-eclampsia	Antihypertensive drugs versus each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (218) [43]	Development of pre-eclampsia	Bed rest/hospital admission versus no hospital admission	4	–2	0	0	0	Low	Quality points deducted for uncertainty about bias and for differences in frequency of blood pressure measurement
1 (218) [43]	Preterm birth	Bed rest/hospital admission versus no hospital admission	4	–1	0	0	0	Moderate	Quality point deducted for uncertainty about bias
1 (395) [44]	Development of pre-eclampsia	Bed rest/hospital admission versus day care	4	0	0	0	0	High	
1 (109) [44]	Use of resources	Bed rest/hospital admission versus day care	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of interventions in women who develop severe pre-eclampsia or very high blood pressure during pregnancy?									
3 (10,795 at most) [45] [46] [47]	Mortality	Prophylactic magnesium versus placebo/no anticonvulsant	4	0	0	0	0	High	
6 (11,444) [45]	Seizures	Prophylactic magnesium versus placebo/no anticonvulsant	4	0	0	0	+1	High	Effect-size point added for RR <0.5

Important outcomes	Adverse effects, Child development, Development of pre-eclampsia, Morbidity, Mortality, Need for further interventions, Preterm birth, Seizures, Use of resources								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
5 (6145) [46]	Child development	Prophylactic magnesium versus placebo/no anticonvulsant	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 1 (at least 10,108) [45]	Need for further interventions	Prophylactic magnesium versus placebo/no anticonvulsant	4	0	0	0	0	High	
at least 1 (9992) [47]	Adverse effects	Prophylactic magnesium versus placebo/no anticonvulsant	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (3941) [45]	Seizures	Prophylactic magnesium sulphate versus phenytoin, nimodipine, or diazepam	4	0	0	0	0	High	
unclear (unclear) [45]	Need for further interventions	Prophylactic magnesium sulphate versus phenytoin, nimodipine, or diazepam	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (619) [56] [57] [59] [60]	Seizures	Antiypertensive drugs versus each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between drugs
2 (133) [63]	Mortality	Interventionist care versus expectant management	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
2 (133) [63]	Morbidity	Interventionist care versus expectant management	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for sparse data
1 (216) [65]	Mortality	Plasma volume expansion versus control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in disease severities
1 (216) [65]	Morbidity	Plasma volume expansion versus control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in disease severities
1 (216) [65]	Seizures	Plasma volume expansion versus control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in disease severities
3 at most (61 at most) [64]	Need for further interventions	Plasma volume expansion versus control	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What is the best choice of anticonvulsant for women with eclampsia?									
6 (1336) [68]	Mortality	Magnesium sulphate versus diazepam	4	0	0	0	0	High	
2 (597) [68]	Morbidity	Magnesium sulphate versus diazepam	4	0	0	0	0	High	
7 (1441) [68]	Seizures	Magnesium sulphate versus diazepam	4	0	0	0	0	High	
3 (631) [68]	Use of resources	Magnesium sulphate versus diazepam	4	0	0	0	0	High	
3 (1440) [69]	Mortality	Magnesium sulphate versus phenytoin	4	0	0	–1	0	Moderate	Directness point deducted for the use of composite outcome

Important outcomes	Adverse effects, Child development, Development of pre-eclampsia, Morbidity, Mortality, Need for further interventions, Preterm birth, Seizures, Use of resources								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (775) [69]	Morbidity	Magnesium sulphate versus phenytoin	4	–1	0	–1	0	Moderate	Quality point deducted for incomplete reporting of results
7 (1022) [69] [70] [50]	Seizures	Magnesium sulphate versus phenytoin	4	0	0	0	0	High	
1 (775) [69]	Use of resources	Magnesium sulphate versus phenytoin	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (398) [71] [72]	Mortality	Magnesium sulphate versus lytic cocktail	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
2 (306) [71]	Morbidity	Magnesium sulphate versus lytic cocktail	4	0	0	0	0	High	
3 (397) [71] [72]	Seizures	Magnesium sulphate versus lytic cocktail	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.